Review Article

Myxomatous Degenerative Mitral Valve Disease: An Update

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Abstract

Myxomatous degenerative mitral valve disease (MVD) is the most common cardiac disease in dogs. Pathological changes of MVD include thickened redundant leaflets causing improper coaptation of leaflets, resulting in mitral valve regurgitation. The etiology of this disease is currently unknown. Thus, no drugs or treatments are available to slow down the disease progression. This article was written to summarize an update of canine MVD concerning clinical approach, etiology, and treatment.

Keywords: dogs, cardiac disease, heart, mitral valve, myxomatous degeneration

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บทคัดย่อ

ข้อมูลปัจจุบันเกี่ยวกับโรคลิ้นหัวใจไมทรัลเสื่อมในสุนัข

สิริลักษณ์ ดิษเสถียร

โรคลิ้นหัวใจไมทรัลเสื่อมเป็นโรคหัวใจที่สามารถพบได้มากที่สุดในสุนัข พยาธิสภาพของโรคนี้ ได้แก่ การหนาตัวของลิ้นหัวใจ ซึ่งส่งผลให้เกิดการปิดไม่สนิทหรือการรั่วของลิ้นหัวใจไมทรัล ปัจจุบันสาเหตุที่ทำให้เกิดโรคนี้ยังไม่เป็นที่ทราบแน่ชัด ด้วยเหตุนี้จึงยังไม่มียาหรือการรักษาที่สามารถช่วยชะลอการพัฒนาของโรคที่เกิดขึ้นได้ บทความนี้เขียนขึ้นเพื่อรวบรวมข้อมูลปัจจุบัน เกี่ยวกับโรคลิ้นหัวใจไมทรัลเสื่อมในสุนัข โดยเน้นเกี่ยวกับ การตรวจทางคลินิก สาเหตุของการเกิดโรค และการรักษา

คำสำคัญ: สุนัข โรคหัวใจ หัวใจ ลิ้นหัวใจไมทรัล ลิ้นหัวใจเสื่อม

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Introduction

Myxomatous degenerative mitral valve disease (MVD) or mitral valve endocardiosis is the most common cardiac disease in dogs (Whitney, 1974). It accounts for approximately 40% of cardiovascular diseases seen in dogs (Buchanan, 1999). The prevalence of MVD in dogs is age related. Approximately 58% of dogs aged 9 years old and older have marked pathologic changes of MVD (Whitney, 1974). The degeneration mostly affects the mitral valves, but the tricuspid valves can be also affected. Small breed dogs including Cavalier King Charles spaniels, Miniature poodles, Cocker spaniels, Miniature schnauzers, Dachshunds, Pomeranians, Chihuahuas, Pekingese, Fox terriers and Boston terriers as well as mixed breed dogs are predisposed to this disease. Several studies have indicated that males are more affected than females (Buchanan, 1977; Pederson and Häggström, 2000). However, the ratio of male to female affected dogs has been found to vary by the population of dogs in each study. The pathological changes of MVD include thickened redundant leaflets characterized by glycosaminoglycan (GAG) deposition, collagen bundle disorganization and elastic fiber fragmentation with an increased number of valve interstitial cells (Disatian et al., 2008). The chordae tendineae are commonly elongated and occasionally rupture (Das and Tashjihan, 1965; Kogure, 1980; Kvat and Häggström, 2000). The septal (anterior) leaflet is more prone to degeneration and prolapse than the mural (posterior) leaflet in dogs (Terzo et al., 2009). These pathological changes cause an improper coaptation of leaflets leading to regurgitant flow back into the left atrium during ventricular systole. The resultant severe mitral valve regurgitation causes progressive congestive heart failure and death. Several complications have been found with MVD including cardiac arrhythmia (especially those originating in enlarged left atrium), chordal rupture, left atrial rupture and pulmonary hypertension. The prevalence and severity of pulmonary hypertension have been found to be strongly associated with the progression of canine MVD (Serres et al., 2006; Chavegato et al., 2009).

Clinical approach

The clinical signs of dogs affected with MVD include signs of left sided congestive heart failure such as exercise intolerance, cough, dyspnea and syncope. Cough is usually associated with an elevation of the left main stem bronchus secondary to left atrial enlargement resulting from mitral valve regurgitation. The cough is generally described as a hacking dry cough which often occurs after exercise and excitement or at night. Some brachychalic breed dogs such as Pug may have concurrent tracheal stenosis, bronchitis, or other respiratory problems which can cause coughing. Therefore, the diagnosis of MVD should be performed carefully to rule out the exact underlying cause of the cough. Syncope may be related to insufficient forward flow, pulmonary hypertension and/or cardiac arrhythmias (Pedersen and Häggström, 2000). A major finding in physical examination of MVD dogs is a systolic murmur loudest at the apex of the heart on the left thorax secondary to mitral valve regurgitation. Precordial thrill can also be palpable in dogs with severe mitral valve regurgitation. The intensity of murmurs can be used to subjectively evaluate the severity of degeneration secondary to its strong correlation with the severity of valvular thickening and the size of left cardiac chambers assessed by echocardiography (Häggström et al., 1995).

Electrocardiographic findings are usually non specific. P-mitrale (widen P-wave) and widen QRS complex may be seen secondarily to an enlarged left atrium and left ventricle, respectively. Thoracic radiography usually shows cardiomegaly with predominant left sided enlargement. The left atrium may enlarge and compress or elevate the left main stem bronchus. Pulmonary venous congestion is commonly seen with pulmonary edema lung pattern especially at perihilar area.

Echocardiography provides the evidence of mitral valve thickening, mitral valve regurgitation, left atrial and ventricular chamber enlargement. The severity of mitral valve regurgitation can be assessed by determining the regurgitant jet flow in the left atrium with color-Doppler mapping (Pedersen et al., 1999). The anterior leaflet or septal leaflet is more prone to degeneration. Therefore, the thickened and irregular anterior leaflet is easy to see by echocardiography. The disease progression can be determined by left atrial enlargement and left ventricular systolic dysfunction secondary to chronic volume overload resulting from mitral valve regurgitation. The systolic function of left ventricle is easily evaluated by calculating the fractional shortening and measuring the size of end systolic left ventricular dimension. The percentage of fractional shortening is the difference between the end-diastolic and end-systolic dimensions divided by the end-diastolic dimension x100. Fractional shortening is preload dependent. It may be normal secondary to an increase of both end systolic and end diastolic chamber dimensions. Thus, it is better to determine systolic myocardial function by assessing the end systolic dimension or end systolic volume index also.

Etiology

To date, the exact mechanisms of spontaneous MVD are still unclear. MVD is suggested to be an inherited disease in some dog breeds (Sweson et al, 1996; Olsen et al., 1999). The repeated mechanical stress on mitral valve leaflets is also thought to be a cause of myxomatous degeneration (Pederson and Häggström, 2000). This repeated impact may influence the synthesis and release of vasoactive substances such as endothelin that may stimulate myxomatous changes (Mow and Pederson, 1999). Valve interstitial cells, a major cell type in heart valves, normally have responsibilities for mediating extracellular matrix (ECM) turnover by secreting ECM and catabolic enzymes such as matrix metalloproteinases (MMPs) (Rabkin et al., 2001). An imbalance in ECM turnover due to changes in valve interstitial cell properties may be a cause of myxomatous degeneration. A recent study by Disatian et al. (2008) has demonstrated that valve interstitial cells from dogs with naturally-occurring MVD undergo phenotype transformation which strongly correlates with disease stage and progression. Two distinct patterns of phenotype transformation were found. One characterized the expression of α-smooth muscle actin (α-sma) and occurred in cellular clusters predominately in the atrialis (myofibroblasts), and one characterized by the expression of non-muscle embryonic myosin and distributed throughout all valve layers (activated mesenchymal cells). However, roles of these transformed valve interstitial cells in the degenerative process are unclear. Several researchers have suggested that these transformed cells may have roles as activators of degeneration. Some investigators believe that the transformation of valve interstitial cells may be a secondary change in response to the diseased process.

Several lines of evidence implicate serotonin as a cause of valvulopathy in humans and other species. Carcinoid disease results in high circulating levels of serotonin and causes valvulopathy in the right heart valves (left heart valves are thought to be protected by serotonin metabolism in the lungs) (Rajamannan et al., 2001). Rats injected daily with serotonin develop pathological changes in the aortic valves (Gustafsson et al., 2005). Fen/Phen valvulopathy in humans has been attributed to the combination of a serotonin agonist effect by fenfluramine and monoamine oxidase inhibition by phentermine (Connally et al., 1997). An up-regulation of serotonin signaling proteins and mRNA in naturally occurring canine MVD suggests the association between serotonin signaling and the pathogenesis of this disease (Oyama and Chittur, 2006; Disatian and Orton, 2009). A recent study by Arndt et al. (2009) also demonstrated a significantly higher serum serotonin concentration in dogs affected with MVD compared to healthy dogs supporting an association of serotonin and the pathogenesis of canine MVD. An up-regulation of tryptophan hydroxylase 1, a key enzyme of serotonin synthesis has been found in canine myxomatous valve interstitial cells suggesting that valve interstitial cells may have a role in producing serotonin during the disease process (Disatian and Orton, 2009). The serotonin transmembrane transporter (SERT), a key structure required for serotonin uptake and metabolism has been found down- regulated in dogs affected by MVD (Disatian and Orton, 2009; Scruggs et al., 2009). On the other hand, an apparent increase in 5HT2BR protein expression has been found in spontaneous canine myxomatous mitral valves (Disatian and Orton, 2009). These findings have been attributed to decreased serotonin metabolism and increased availability to serotonin receptors that compete with SERT for serotonin binding maybe leading to an increase in downstream serotonin signaling.

Transforming growth factor β (TGF β) is another signaling pathway that has been proposed to be involved with the pathogenesis of MVD secondary to a closed link between serotonin and TGF β signaling. Overexpression of TGFβ1 proteins has been demonstrated in spontaneous human (Park et al., 2009) and canine MVD (Aupperle et al., 2008; Disatian and Orton, 2009). The mRNA expression of numerous downstream TGF β significantly increases in canine myxomatous valves compared to normal valves (Oyama and Chittur, 2006). In cultured valve interstitial cells, TGFβ1 can increase α-smooth muscle

actin (α-sma) expression (a putative maker of phenotype transformation) (Cushing et al, 2005; Park et al, 2009; Walker et al., 2004), increase collagen and GAG synthesis (Jian et al., 2002) as well as regulate cultured valve interstitial cell proliferation and apoptosis (Liu and Gotlieb, 2008). The role of TGFβ1 signaling in canine myxomatous mitral valves is unexplored.

Treatment

The definitive treatment for mitral valve degeneration in human is surgical repair or replacement of damaged valves (Braunwald, 1997). However, secondary to the expense of cardiac bypass surgery, mitral valve surgery has been performed in just a few hospital case dogs (Boggs et al., 1996; Griffiths et al., 2004; Orton et al.. 2005). A purse string suture is another technique that could reduce the enlarged mitral orifice. This technique is not required a bypass operation. Therefore, it might be used as a palliative treatment in dogs affected by MVD with severe mitral valve regurgitation (Hamlin et al., 2000). Presently, no drugs or treatments can slow the progression of myxomatous degeneration. Thus, the current treatment goal of dogs affected by MVD is to reduce the effect of circulatory disturbances rather than to treat actual lesions.

Because data obtained in human trials show that early intervention with an ACE inhibitor may delay the development of congestive heart failure (The SOLVD investigators, 1992), several veterinarians have increased their interest in using ACE inhibitors as cardioprotective therapy to postpone or prevent congestive heart failure in dogs affected by early mitral valve disease. However, a previous Scandinavian study of 229 asymptomatic Cavalier King Charles spaniels (CKCS) with mild mitral valve regurgitation has shown that long term ACE inhibitor application did not delay the onset of congestive heart failure in asymptomatic CKCS with mild mitral valve regurgitation (Kvart et al., 2002). Using an experimental induced mitral valve regurgitation dog model, the administration of ACE inhibitors failed to improve left ventricular remodeling and function (Dell'Italia, 2002; Perry et al., 2002); whereas, the most recent retrospective study demonstrated that ACE inhibitors have some beneficial effects including a decreased risk of death and a prolonged asymptomatic period in asymptomatic dogs other than CKCS and King Charles spaniels affected by MVD with moderate to severe mitral valve regurgitation (Pouchelon et al., 2008). Because of the conflict among studies and insufficient supporting data, the effect of ACE inhibitors upon the onset of heart failure and cardiac remodeling is still uncertain. On the other hand, it has been known for more than 10 years that ACE inhibitors have some benefits for the treatment of symptomatic MVD dogs including improving clinical signs and quality of life, increasing survival times and prolonging the time to treatment failure (The COVE study group, 1995; The IMPROVE study group, 1995; Kitagawa et al., 1997; LIVE study group; 1998; BENCH study, 1999; Amberger et al., 2004). In human patients, spinorolactone, an aldolsterone antagonist has been used in combination with ACE inhibitors secondary to numerous actions including decreasing cardiac fibrosis, decreasing cardiac norepinephrine release, antagonizing the action of aldosterone and has vasodilator properties (Pitt et al., 1999; Weber, 1999; Farquharson and Struthers, 2000; Linen and Petrov, 2000). In addition, spinorolactone may inhibit aldosterone production in case of aldosterone escape in human patients treated with ACE inhibitors (Staessen et al., 1981). In dogs, spinorolactone is a weak diuretic agent. Previous studies have failed to show the diuretic effects of spinorolactone in healthy dogs (Jeunesse et al., 2007) and healthy greyhounds treated in combination with furosemide (Riodan and Estrada, 2005). The effects of spinorolactone as diuretic and cardioprotective agent are yet unproved in naturally occurring MVD dogs. Furosemide is another diuretic that has been widely used in conjunction with ACE inhibitors especially in MVD dogs that have signs of heart failure such as pulmonary edema. The resistance to long term therapy with furosemide treatment maybe develops secondarily to the adaptation of functional and structural downstream nephron segments (De Bruyne, 2003). Thus, second or third diuretics with different mechanisms of action such as hydrocorthiazides and/or potassium sparing diuretics may be used in combination with furosemide to increase the efficacy of diuresis in a subsequent course of treatment for canine MVD, particularly in dogs with a refractory stage of congestive heart failure. Beta-blockers are other drugs being used by some veterinary cardiologists as cardioprotective agents for dogs affected by MVD. These drugs have the efficacy to protect the heart from effects of sympathetic nervous system such as controlling heart rate and reducing the contraction force. A long-term administration of beta-blockers e.g. carvedilol and atenolol has been shown to improve hemodynamic, contractile function, and renal function in chronic iatrogenic mitral regurgitation experimental dogs (Uechi et al., 2002). The effects of beta-blockers on improving myocardial function and reducing cardiac remodeling have not yet been demonstrated in asymptomatic dogs with spontaneous MVD. In symptomatic canine MVD, carvedilol in combination with conventional therapy failed to decrease sympathetic activation and improve cardiac remodeling over 3 months of treatment but did improve quality of life and reduce systolic blood pressure. However, the dose of carvedilol used in this study was quite low (0.3 mg/kg) and may be not enough to antagonize the effect of sympathetic stimulation. Thus, the efficacy of beta blockers in dogs with naturally occurring MVD with and without clinical signs is still uncertain and needs further studies for clarification. Pimobendan, a phosphodiesterase III inhibitor and calcium sensitizer is an emerging drug which is of interest to several cardiologists. However, the effects of this drug on canine MVD are the subject of ongoing studies. The recent study by Chetboul et al. (2007) suggested that pimobendan should be used with caution secondarily to its adverse effects on dogs with asymptomatic MVD by worsening valve degeneration. In addition,

Ouellet et al. (2009) found that pimobendan had no beneficial long term effects in reducing regurgitant fraction, increasing ejection fraction and decreasing end systolic dimension when used in combination with ACE inhibitors in asymptomatic MVD dogs (Ouellet et al., 2009). On the other hand, pimobendan in combination with conventional therapy could prolong the time to sudden death and treatment failure compared with ACE inhibitors plus conventional therapy, in symptomatic MVD dogs with congestive heart failure (The QUEST study, 2008). Taken together, it may be more suitable to add pimobendan to conventional therapy in MVD dogs with clinical signs of heart failure rather than to MVD dogs without clinical signs.

Conclusions

In conclusion, canine MVD is the number one acquired heart disease in dogs. Although MVD is a common disease easily found in veterinary hospitals, its etiology is still unknown. To date, treatments goals have been to correct circulatory disturbances secondary to mitral valve regurgitation, improve quality of life and prolong survival time. A better understanding in the pathogenesis of valve degeneration will guide a treatment protocol to treat the actual lesions as well as to prevent the degenerative progression rather than to control resultant circulatory disturbances which may help MVD dogs to have a better quality of life with a longer time before developing heart failure or death.

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